CLAIMS

1. Use of the determination of p53 (*TP53*) status in a subject having a proliferative disease as a biomarker for determining the sensitivity of said subject to a treatment with an mTOR inhibitor in combination with a cytotoxic agent.

2. Use according to claim 1, comprising the use of p53 (*TP53*) gene analysis and the level of expression/post-translational modification of p53.

3. A method for determining the sensitivity of a proliferative disease in a subject to a combined treatment with an mTOR inhibitor and a cytotoxic agent, comprising determining the status of p53 (*TP53*) gene and/or the level of expression/post-translational modification of p53 in a sample derived from the subject.

4. A method or use according to any preceding claim, wherein the proliferative disease comprises a cancer.

5. A method according to any of claims 3 to 4, comprising determining the genetic status of p53 (*TP53*) and/or the level of expression of p53.

6. A method according to any of claims 3 to 5, wherein the sample is derived from a tumor in the subject.

7. A method of selecting subjects suffering from a proliferative disease for a combined treatment with an mTOR inhibitor and a cytotoxic agent, comprising determining the sensitivity of the proliferative disease to the combined treatment in each subject by a method as described in any of claims 3 to 6, and selecting those subjects showing wild-type p53 (*TP53*) status for the combined treatment.

8. A method or use according to any preceding claim, wherein the mTOR inhibitor comprises rapamycin or a rapamycin derivative.

9. A method or use according to claim 8, wherein the rapamycin derivative comprises 40-O-(2-hydroxyethyl) rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin or 40-epi-(tetrazolyl)-rapamycin.

10. A method or use according to any preceding claim, wherein the cytotoxic agent is selected from an antineoplastic antimetabolite, a platin compound, an alkylating agent, a topoisomerase I or II inhibitor, a microtubule active agent and irradiation.

11. Use of p21 as a biomarker for determining the sensitivity or response of a proliferative disease in a subject to treatment with an mTOR inhibitor in combination with a cytotoxic agent.

12. Use according to claim 11, comprising determining the level of p21 expression.

13. A method for determining the sensitivity or response of a proliferative disease in a subject to a treatment with an mTOR inhibitor in combination with a cytotoxic agent, comprising determining in a sample derived from the subject the level of p21 expression after treatment with the cytotoxic agent alone and after a combined treatment of the cytotoxic agent with an mTOR inhibitor.

14. A method for enhancing the activity of a cytotoxic agent or for overcoming resistance to a cytotoxic agent in a subject treated with said cytotoxic agent, comprising

- determining the level of p21 expression in a sample derived from the subject,
- if p21 expression is upregulated after administration of a cytotoxic agent, administering to said subject a therapeutically effective amount of an mTOR inhibitor in combination with the cytotoxic agent,
- determining again the level of p21 expression in a new sample derived from the subject after the treatment with the combination of the mTOR inhibitor and the cytotoxic agent, and
- if p21 expression is downregulated, further treating the subject with the mTOR inhibitor either concomitantly or sequentially with said cytotoxic agent.